B3

52. (amended) The plant cell of claim 43 wherein the polypeptides of the multimeric protein are joined by hydrogen bonding.

B4

61. (amended) The plant cell of claim 43 wherein the cell is a dicotyledonous plant cell.

62. (amended) The plant cell of claim 43 wherein the cell is a monocotyledonous plant cell.

Please add the following new claims:

B5

--65. (New) The method of claim 21, wherein the leader sequence is a non-native leader sequence.

66. (New) The method of claim 65, wherein the leader sequence is a yeast leader sequence.

67. (New) The method of claim 65, wherein the leader sequence is a plant leader sequence.

68. (New) The method of claim 21, wherein the leader sequence is heterologous to the nucleic acid sequence encoding the multimeric protein.--

REMARKS

These remarks are in response to the Office Action mailed December 13, 2000. Applicants submit that the amendments to the claims are for clarity and should not be construed as amendments affecting patentability under *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558, 56 USPQ2d 1865 (Fed. Cir. 2000) (en banc). Claim 41 has been canceled without prejudice. Thus, upon entry of the amendment, claims 21-40 and 42-68 are under examination.

Applicants thank the Examiner for noting that the instant application was filed with informal drawings which are acceptable for examination purposes. Accordingly, Applicants will file formal drawings upon allowance of the instant application.

Objections to the Specification

The Action has requested an update of status for all parent priority applications. Accordingly, by way of amendment to the cross-reference section of the application, as noted above, Applicants have updated the status of all parent priority applications. Thus, Applicants respectfully submit that this requirement has now been met.

Double Patenting

Claims 21-64 stand provisionally rejected for obviousness-type double patenting as being unpatentable over claims 21-30 and 36-37 of co-pending U.S. Application No. 09/199,534. The Action states that although the claims are not identical, they are not patentably distinct because the claims the claims of the instant application allow for the inclusion of a leader sequence as in 09/199,534. Furthermore, it would have been obvious to utilize the methods set forth in claims 36-37 of the 09/199,534 application to make the claimed product since the method simply introduces the nucleotides containing the gene of interest into the claimed transgenic plant, and thus would not be patentably distinct from the transgenic plant.

Applicants respectfully traverse this ground for rejection. However, without acquiescing to this ground of rejection and solely in order to facilitate prosecution, upon allowance a Terminal Disclaimer will be filed to obviate this ground of rejection.

Claims 21-64 stand provisionally rejected for obviousness-type double patenting as being unpatentable over claims 21 and 32-78 of co-pending U.S. Application No. 09/200,657. The Action states that although the conflicting claims are not identical, they are not patentably

distinct from each other because of immunoglobulin and antibodies are prototypic and main species of multimeric proteins.

Again, Applicants respectfully disagree and traverse this ground for rejection and a Terminal Disclaimer will be filed upon allowance of the pending claims to obviate this ground of rejection.

Claims 21-64 stand rejected for obviousness-type double patenting as being allegedly unpatentable over claims 6-12 of U.S. Patent No. 5,959,177. The Action alleges that although the conflicting claims are not identical, they are not patentably distinct from each other because of the genus-species relationship. Thus, the Action concludes, the scope of the claims of the instant application is rendered obvious by the patented claims.

Again, Applicants respectfully disagree and traverse this ground for rejection and a Terminal Disclaimer will be filed upon allowance of the pending claims to obviate this ground of rejection.

Claims 21-64 stand rejected for obviousness-type double patenting as being allegedly unpatentable over claims 1-5 of U.S. Patent No. 5,202,422. Although the conflicting claims are not identical, they are not patentably distinct from each other because immunoglobulins are the prototypic and main species of glycopeptide multimeric proteins which are used to induce passive immunity.

Again, Applicants respectfully disagree and traverse this ground for rejection and a Terminal Disclaimer will be filed upon allowance of the pending claims to obviate this ground of rejection.

Claims 21-64 stand rejected for obviousness-type double patenting as being allegedly unpatentable over claims 1-7 of U.S. Patent No. 5,639,947. Although the conflicting claims are not identical, they are not patentably distinct from each other because immunoglobulin species of the patent allegedly renders obvious the multimeric protein genus of the present invention.

Applicants respectfully disagree and traverse this ground for rejection and a Terminal Disclaimer will be filed upon allowance of the pending claims to obviate this ground of rejection.

I. REJECTIONS UNDER 35 U.S.C.§112

Claims 30, 41, 52, and 61-63 stand rejected under 35 U.S.C. §112, second paragraph. In view of cancelation of claim 41, the rejection is moot with respect to that claim.

Claims 30 and 52 have been amended to more clearly describe what is joined by hydrogen bonding, the polypeptides of the multimeric protein.

Claims 61-63 have been amended specifically removing the term "derived" or "derivative" from the rejected claims. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §§102 and 103

Claims 21, 22,24-26, 29-39, 42-44, 46-48, 51-61 and 64 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by During (Doctoral Dissertation). The Action asserts that During teaches a transgenic tobacco plant comprising cells which contain and express nucleotide sequences encoding an anti-NP-IgM antibody, which is a heteromultimeric protein. Applicants respectfully traverse this ground for rejection.

As an initial matter, Applicants urge that the cited dissertation does not anticipate the claimed invention as it fails to disclose transgenic plants including the claimed nucleotide sequences or the multimeric protein, e.g., immunoglobulin products generated thereby. Further, the currently pending claims recite differences that clearly distinguish them from the During art. More specifically, the requirement for cleavage of the leader sequence. In addition, the cited dissertation does not meet the requirements of 35 U.S.C. § 102(b), largely because it fails to provide an enabling disclosure.

The Court of Appeals for the Federal Circuit has repeatedly recognized that anticipation requires that each and every element of the claimed invention be disclosed in the prior art reference and that the prior art reference be enabling, thus placing allegedly disclosed matter in the possession of the public. (*See, e.g., Akzo N.V. v. U.S. International Trade Commission*, 808 F.2d 1471, 1 USPQ2d 1241 (Fed. Cir. 1986), *certiorari denied*, 107 S. Ct. 2470, 96 L. Ed. 2d 382; *also see Hybritech Inc. v. Monoclonal Antibodies Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986).)

While During, in his dissertation, claims to introduce and express both a heavy chain and a light chain in a plant cell, support for such a claim is equivocal at best, as discussed further below. In fact, a close review of the During dissertation reveals that absolutely no data is presented which unquestionably supports a conclusion that assembled, functional multimeric proteins, e.g., immunoglobulin products, are produced and present in the plant cells.

Therefore, for all the foregoing reasons, Applicants respectfully submit that these grounds of rejection have been overcome and thus request their withdrawal.

Claims 21-27, 29-40,42-49, 51-62 and 64 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Goodman (U.S. Patent No. 4,956,282). In particular, the Action alleges that Goodman teaches transformation of monocots and dicots by introducing a vector containing nucleotide sequences encoding interferon (homomultimer), enzymes and immunoglobulin heavy and light chins for expression of immunoglobulins (heteromultimer). Applicants respectfully traverse this ground for rejection and submit that the currently claimed invention is clearly not anticipated by Goodman.

It is well supported tenet of patent law, that a reference cannot anticipate a claim unless it sets forth each and every limitation of the claimed subject matter. Further, in order to be useable as prior art at all, the reference must be enabled for that which it is relied upon to teach. With this in mind, Applicants respectfully submit that Goodman is neither enabled for the broad teaching the Examiner accords it nor does Goodman teach each and every element of the claimed invention.

Within the entire specification of Goodman, there is no other discussion of production of multimeric proteins or immunoglobulins. Rather, Goodman expresses a single chain polypeptide in a plant cell, but does not describe the expression and assembly of any multimeric protein or immunoglobulin products. In other words, the Goodman reference speculates by the single above-quoted sentence that immunoglobulin heavy and light chains could be expressed and assembled in a plant cell. At best, Goodman provides an invitation for further experimentation. Further, Goodman is completely silent with respect to a plant, comprising (a) plant cells containing nucleotide sequences encoding one or more biologically functional multimeric proteins not normally produced by the plant, wherein each nucleotide sequence encoding a multimeric protein *encodes a leader sequence forming a secretion signal that is cleaved from said multimeric protein following proteolytic processing*; and (b) biologically functional multimeric proteins encoded by said nucleotide sequence.

In other words, contrary to the assertions of the Action, Goodman does not provide "sufficient guidance to enable one skilled in the art to use the methods for the production of multimeric proteins". Goodman fails to provide any guidance whatsoever to solve the particular problem of expression and assembly of multimeric protein products, e.g., immunoglobulins or enzymes in plants. Specifically, Goodman is deficient in that it does not teach each nucleotide sequence encoding a multimeric protein encoding a leader sequence forming a secretion signal that is cleaved from the multimeric protein following proteolytic processing. Accordingly, Applicants respectfully request that this rejection been withdrawn.

Claims 21-64 stand rejected under 35 U.S.C. ∋103 as allegedly unpatentable over During and further in view of "Applicant's admitted prior art". Applicants respectfully traverse this ground for rejection and submit that the currently claimed invention is not rendered obvious by During, either when taken alone or in combination. Further, Applicants are unaware of any statements on the record regarding "admitted prior art". Applicants have submitted references in the form of an IDS and will admit that the publication date of many of those references predate Applicants filing date.

The Action alleges that the During reference provides teachings for making heteromultimeric proteins with a reasonable expectation of success. As discussed above, During neither teachings nor suggests a plant, comprising (a) plant cells containing nucleotide sequences encoding one or more biologically functional multimeric proteins not normally produced by the plant, *wherein each nucleotide sequence encoding a multimeric protein encodes a leader sequence forming a secretion signal that is cleaved from said multimeric protein following proteolytic processing;* and

(b) biologically functional multimeric proteins encoded by said nucleotide sequences.

The teachings in During could not have rendered the claimed invention obvious due to the conficting results obtained by During and those obtained by the present inventors. During struggled to obtain immunologically detectable levels of expression, noting:

"A method therefore had to be developed that permits the sought protein to be enriched from the crude extract before Western blot or preferably to be isolated and concentrated to detectable concentrations" (page 87, last full paragraph). "By direct Western blotting from the crude extract of calli or induced plant material, only unsatisfactory results can be achieved" (page 89, first sentence of first full paragraph). "The difficult reproducibility of biological material is particularly clear in these analyses, precisely when inductions are carried out. The total found amounts of antibody protein lies in the lowermost range of the detection limits and therefore form only a very limited fraction of the total protein of the transformed plants." (page 89, last full paragraph) (All Page numbers used in the discussion immediately above are based upon the fully translated version of the During Dissertation submitted herewith).

Contrary to the ineffective strategy set forth by During the present inventors achieve clearly detectable and useful levels of immunglobulins in crude extracts. For example, representative expression of 200 to 500 micrograms of SIgA-G per gram of plant material (See, *e.g.*, instant specification page 99, lines 22-23) and 2 to 1400 ng/mg of plant protein for IgG chains (See, *e.g.*, instant specification page 68, lines 15-26) is evidenced by the instant specification.

The unexpected and surprising results of using plants to process, assemble, and secrete multimeric protein products by the methods set forth in the present application is not only supported by the instant specification, but also by the fact that the results were so surprising that the present inventor's work was featured on the cover of the prestigious journal Nature (Nov 2;342(6245):76-78, 1989).

Accordingly, given the above remarks, it is clear that not only does During lack an enabling disclosure and teach away from the present invention, but the results obtained by the present inventors were clearly unexpected and surprising to the scientific community, especially in light of the lack of success demonstrated by During. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Claims 21-64 stand rejected under 35 U.S.C. ∋103 as allegedly unpatentable over Goodman and further in view of "Applicant's admitted prior art". Applicants respectfully traverse this ground for rejection and submit that the currently claimed invention is not rendered obvious by During, either when taken alone or in combination. Further, Applicants are unaware of any statements on the record regarding "admitted prior art". Applicants have submitted references in the form of an IDS and will admit that the publication date of many of those references predate Applicants filing date.

The Office Action alleges that it would have been obvious to transform monocots, dicots or algae and express antibodies using the method of Goodman with a reasonable expectation of success. Applicants respectfully disagree with the statements in the Office Action. First, the Goodman reference contains one statement regarding immunoglobulins (See column 3, lines 11-30). However, within the entire specification of Goodman, there is no other discussion of multimeric proteins or immunoglobulins. Rather, Goodman expresses a single chain polypeptide in a plant cell, but does not describe the expression and assembly of any multimeric protein products. In other words, the Goodman reference speculates by the single above-quoted sentence that immunoglobulin heavy and light chains could be expressed and assembled in a plant cell. At best Goodman provides an invitation for further experimentation and does not teach a cleavable leader sequences which Applicants have shown are essential to producing biologically active immunoglobulin molecules for use in the claimed invention.

In other words, contrary to the assertions of the Office Action, Goodman does not provide sufficient motivation or suggestion for one skilled in the art to use the methods for the production of multimeric proteins, including immunoglobulins, because Goodman does not describe procedures for production of any immunoglobulin product at all. Thus, Goodman does not provide any guidance whatsoever to solve the particular problem of expression and assembly of multimeric protein products in plants for any use.

It is pertinent to note that the specification of the Goodman patent has been interpreted relatively narrowly with respect to enablement. In the case *In re Goodman*, 29 U.S.P.Q.2nd 2010, 2013 (Fed. Cir. 1993), the Federal Circuit opined upon the disclosure of a continuation of the herein cited patent and noted that "Goodman's specification contains a single example of producing gamma-interferon in the dicotyledonous species, tobacco. This single example, however, does not enable a biotechnician of ordinary skill to produce any type of mammalian protein in any type of plant cell." Accordingly, the breadth of enablement accorded Goodman by the Examiner is inconsistent with its judicial interpretation and thus this reference should not be viewed as teaching anything in particular with respect to production of immunglobulins in plants.

In addition, Goodman remains deficient in that it does not teach each nucleotide sequence encoding an immunoglobulin polypeptide encoding a leader sequence forming a secretion signal that is cleaved from the immunoglobulin polypeptide following proteolytic processing.

The combination of Goodman with other prior art cannot remedy the deficiencies of Goodman to teach nucleotide sequences encoding a multimeric proteins encoding a leader sequence forming a secretion signal that is cleaved from said multimeric protein following proteolytic processing as claimed in the present invention. Accordingly, Applicants respectfully request withdrawl of this rejection.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 21-40 and 42-70 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 677-1456. Please charge any additional fees, or make any credits, to Deposit Account No. 07-1895.

Respectfully submitted,

Date: 6/13/01

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Version with Markings to Show Claim Amendments

(amended)

21. A plant, comprising:

(a) plant cells containing nucleotide sequences encoding one or more biologically functional multimeric proteins not normally produced by the plant, wherein each nucleotide sequence encoding a multimeric protein encodes a leader sequence forming a secretion signal that is cleaved from said multimeric protein following proteolytic processing; and

(b) biologically functional multimeric proteins encoded by said nucleotide sequences.

(amended)

30. The plant of claim 21 wherein the polypeptides of the multimeric protein [is] are joined by hydrogen bonding.

(amended)

52. The plant cell of claim 43 wherein the polypeptides of the multimeric protein [is] are joined by hydrogen bonding.

61. (amended) The plant cell of claim 43 [derived from] wherein the cell is a dicotyledonous plant cell.

62. (amended) The plant cell of claim 43 [derived from] wherein the cell is a monocotyledonous plant cell.

Please add the following new claims:

--65. (New) The method of claim 21, wherein the leader sequence is a non-native leader sequence.

66. (New) The method of claim 65, wherein the leader sequence is a yeast leader sequence.

69. (New) The method of claim 65, wherein the leader sequence is a plant leader sequence.

70. (New) The method of claim 21, wherein the leader sequence is heterologous to the nucleic acid sequence encoding the multimeric protein.--